Keratoconus
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Introduction: Keratoconus is a non-inflammatory ectatic corneal disorder of uncertain etiology which is usually bilateral and progressive. Progressive corneal thinning results in irregular astigmatism, myopia and later, conical protrusion of cornea when it is evident on clinical examination.

Prevalence and distribution: Among the various corneal ectasias, it is the commonest with a prevalence of 54.5 per 100,000 and an incidence of 1 in 2000 per year. The true incidence, as demonstrated by corneal topography however is likely to be within 1 in 600 to 1 in 420. It is bilateral in 96% of cases. Abortive form or ‘forme fruste keratoconus’ is often seen in the family members or the fellow eye.

Etiological factors: Despite extensive study, we are indeed far from understanding the exact underlying pathological mechanism of keratoconus. It is believed that corneal thinning may be due to defective formation or destruction of extracellular matrix and abnormal collagenase activity as evidenced by altered levels of fibronectin and type 4 collagen. Biochemical and immunohistological studies have shown increased levels of proteases and other catabolic enzymes in the basal epithelial cells of keratoconic eyes. Decreased levels of proteinase inhibitors, α1 proteinase inhibitor and α2 macroglobulin have also been noted in the corneal epithelium. Excessive eye rubbing or atopic eye disease might induce keratoconus by inducing epithelial damage. Epithelial stress can lead to increased keratocyte apoptosis through an interleukin-1 dependant mechanism and can cause changes in stromal matrix.

Over twenty publications are there in literature supporting the alteration in protease activity. Teng postulates that keratoconus is primarily a disease of the ectodermal layer of the cornea [epithelium] and corneal stroma is only secondarily affected when disruption of basal epithelial cells occurs. But this theory fails to explain the low recurrence rate after corneal transplantation.

In about 6–15% of patients with keratoconus, family history is present. High astigmatism, mildly irregular mires, inferior corneal steepening and substantial asymmetry in the central dioptric power between the two eyes are seen in family members of patients with keratoconus and have been suggested to represent variable forms of expression of the gene. Pedigree analysis in these families suggests an autosomal dominant mode of inheritance. However, discordance seen between monozygotic twins suggests highly variable expression. Though the genetic basis for most forms of keratoconus remain poorly defined, about seven loci have been mapped. In the keratoconic cornea, a possible genetic predisposition to increased sensitivity to apoptotic mediators by keratocytes has also been hypothesized.

Keratoconus is seen in association with other systemic and ocular diseases. Atopy and eye rubbing has long been associated. Harrison RJ et al, in a clinic-based study of 67 patients found that atopic disease, either present or past was found in 56.7% and further 11.9% had evidence of atopy in the form of highly elevated IgE without clinical disease. But keratoconus patients with or without atopy did not differ significantly with regard to sex, age of onset or rate of keratoplasty. They also found that atopy was more common in bilateral...
disease and keratoconus occurred more frequently on the side of the dominant hand.

Collaborative Longitudinal Evaluation of Keratoconus (CLEK) study found that at baseline, 53% of patients had a history of atopy. Rahi et al also found a definite history of atopy in 35% compared with 12% in the matched control group in a large controlled study. Keratoconus is also associated with non-inflammatory connective tissue disorders like Ehler-Danlos syndrome and osteogenesis imperfecta. An increased prevalence of hypermobility of joints, mitral valve prolapse and false chordae tendineae in left ventricle has also been reported in keratoconus patients. Also there is association with Down's syndrome, congenital hip dysplasia, floppy eye lid syndrome, Marfan's syndrome, Turner's syndrome and Apert's syndrome.

Association has also been found with ocular pathology like retinitis pigmentosa and Leber's congenital amaurosis, probably related to eye rubbing. Literature also describes association with Fuch's endothelial dystrophy, posterior polymorphous dystrophy and stromal dystrophies like granular and lattice.

Among the various incriminated etiological factors and associations - atopy, age, sex, race, eye rubbing, mitral valve prolapse, handedness, collagen vascular disease, ocular trauma, pigmented retinopathy, Marfan's syndrome, Down's syndrome and history of contact lens wear, Bawazeer AM et al found that only eye rubbing is a significant predictor of keratoconus in a multivariate analysis. In the same case-control study comprising 120 subjects, in addition, atopy and family history of keratoconus showed an association in univariate analysis.

**Pathogenesis:** It is important to review the normal corneal structure for better understanding. X-ray diffraction studies have revealed that in the normal cornea, there exist significant differences between anterior one third and posterior two-thirds. In the posterior two-third, lamellae lie in the plane of the cornea, arranged in a parallel fashion and run without interruption from limbus to limbus with minimal interweaving between lamellae. The preferred direction of the posterior lamellae is in the inferior-superior or nasal-temporal direction while no such preference is seen in anterior stroma. At the limbus, collagen fibrils change their course to pursue a circular or pseudocircular course. In the anterior stroma, there is extensive anteroposterior interweave and a portion of lamellae that arise in the limbus insert into the region of Bowman's membrane. This arrangement is believed to be essential for maintenance of corneal shape. Also, the anterior lamellae often split in both lateral and anterior-posterior direction, which may fuse with lamellae running in a different direction. The points at which lamellae split are potentially weak and rely on interfibrillar forces to maintain cohesion. In addition to anteroposterior interweave, there are other elements that bind collagen lamellae together. These are interactions between collagen fibrils and other matrix proteins like proteoglycans, type 6 collagen and keratoepithelin. The interfibrillar space also harbour keratocytes which interact with each other via long processes.

If this interfibrillar glue is weakened, collagen lamellae would have the tendency to tear apart with minimal trauma. Also this would result in displacement of lamellae and thinning of stromal tissue locally. The central and inferior portion is more likely to be affected as interlamellar strength is at a minimum in that area in a normal cornea. When it occurs in the anterior stroma, due to an 'unknown primary event', probably on exposure to proteases, or with minimal trauma or under genetic influence, lamellar sliding and redistribution of stromal mass occurs resulting in ectasia.

Collagen is arranged in lamellae of uniform diameter fibrils. It is formed from pro-collagen, consisting of three α chains with additional amino and carboxy terminal extensions (pro-α chains). Fibrils are constructed from aggregation of collagen molecules after cleaving off pro-collagen peptides. Collagen also undergoes a series of post-translational modifications one of which is the formation of cross-links via enzymatic oxidation of lysine and hydroxyl-lysine residues to their respective aldehydes. These aldehydes condense with other aldehydes or condense with lysine and hydroxyl-lysine residues to form intramolecular or intermolecular covalent cross-links between collagen peptide chains. In keratoconus there is reduced level of lysine hydroxylation and reduced cross linking involving hydroxyl-lysine. The stiffness of keratoconic cornea is only 60% of normal cornea and undergoes pepsin digestion twice as much due to decrease in
cross-links. The new treatment modality, collagen cross linking with riboflavin and ultraviolet-A radiation stiffens the cornea and improves its biomechanical properties by restoring it to a good extent.

Clinical features: Progressive loss of vision is the usual presenting complaint. Glare, aversion to light and monocular diplopia can also occur. High astigmatism with scissoring reflex on retinoscopy is typical.

Prominent corneal nerves are seen frequently. The characteristic finding is an eccentrically located conical protrusion of the cornea. At the apex of the cone, cornea is thinner. Two types of cones are described – [1] round/nipple shaped cone which is central in location and [2] oval/sagging cone which may extend to the limbus and is more prone for contact lens fitting problems.

Fleischer’s ring, a partial or complete annular line seen at the level of epithelium marks the base of the cone and provides a landmark for the peripheral edge of the cone. The ring is formed from hemosiderin pigment deposited in the basal epithelium due to alteration in tear pooling. When faint it is better appreciated with Cobalt blue light by tangential illumination (Fig. 1). As the ectasia progresses the ring becomes narrower and prominent.

Vogt’s striae are fine vertical posterior stromal folds found near the apex of the cone. They disappear on application of pressure to the globe.

Fine linear anterior stromal scars, which develop within the cone due to rupture in Bowman’s layer may be seen. Subtle clear spaces in the anterior stroma have also been described. In more advanced cases deeper opacities can be seen at the apex of cone resulting from dehiscence in Descemet’s membrane (Fig. 2). Corneal hydrops result from stromal imbibition of aqueous through these defects, when sudden drop in vision occurs. Angulation of the lower lid in down gaze may be seen in advanced keratoconus and is called Munson’s sign. A conical reflection on nasal cornea, when light is shined from temporal side – Rizutti’s sign may also be seen. ‘Oil-drop reflex’ may be seen on distant direct ophthalmoscopy.

None of the clinical findings may be present in early keratoconus. Inability to superimpose the central keratometric rings suggests irregular astigmatism as in keratoconus. Placido disk may show crowding of rings inferiorly which indicates corneal steepening.

Corneal Topography: Rabinowitz and McDonnell developed algorithms for the detection of keratoconus based on 3 observations – I/S value [dioptric power difference between superior and inferior paracentral corneal region] > 1.9 D, central corneal power > 48.7 D and difference in progression of corneal...
steepening between two eyes. The method yields a positive result for keratoconus suspect if I/S value is >1.4 D and central corneal power is >47.2 D. Maeda et al have devised a system for autodiagnosis of keratoconus called Klyce-Maeda software based on ten topographic indices with high sensitivity and specificity (Fig. 4).

With Orbscan Topography System, Auffarth et al found that tangential curvature [instantaneous curvature maps] provide better information about the morphology of keratoconus. Also apex of the cone and thinnest point were found to be located separately.

**Histopathology** : Thinning of corneal epithelium with degeneration of basal cells occur early. Disruption of basement membrane with epithelium growing posteriorly into Bowman's layer and stromal collagen growing anteriorly into the epithelium forming Z-shaped interruptions at the level of Bowman's layer, is typical of keratoconus.

Fleischer's ring, a hallmark of keratoconus is found at the base of the cone. Light and electron microscopy reveal that ferritin particles accumulate within and between the cells, particularly in the basal epithelium. Anterior clear spaces and breaks in Bowman's layer are also seen. Within the cone, collagen fibrils are normal-sized but the number of lamellae is abnormally low. By electron microscopy, FLS [Fibrous Long Spacing] collagen with a periodicity of 100 to 110 nm, in contrast to a periodicity of 60 to 64 nm found in normal collagen is seen within the area of corneal thinning.

**Course** : The onset of keratoconus occurs at about puberty which typically progresses over a period of 10 to 20 years after which it stops, though the degree can be highly variable. The rate of progression is also uneven and there can be periods of quiescence in between.

Collaborative Longitudinal Evaluation of Keratoconus (CLEK) study 14,31,32,33 is a 8 year multi center observational study, largest to date, of 1209 keratoconus patients, followed up annually for 8 years. Its goals were to prospectively characterize changes in vision, corneal curvature, corneal status and vision specific quality of life. It found that over 7 years of follow-up, CLEK subjects showed a slow but clear increase in corneal curvature and drop in BCVA under high contrast and low contrast conditions more so in the latter. Also, keratoconus patients are generally RGP CL wearers with moderately steep corneas. Contact lens wear increased the risk of incident scarring in keratoconus more than two-fold. After controlling for disease severity in the form of corneal curvature, a keratoconic eye fitted with a RGP lens resulting in an apical touch fluorescein pattern did not have an increased risk of central scarring at base line. At baseline CLEK [at the onset of study] 13.5 % had a family history of keratoconus and 53 % had a history of atopy. The incidence of connective tissue diseases was not higher in keratoconic individuals. Younger age at baseline and poor high contrast BCVA at presentation predicted the rate of change in corneal curvature. Multivariate analyses of 5-year prospective data from the CLEK Study cohort showed that baseline corneal curvature, contact lens wear, corneal staining, and younger age were predictive of the development of corneal scarring.

**Management** : depends on the stage of the disease. The various modalities are

1] Spectacles
2] Contact lenses – RGP CL
   Scleral lenses – Boston lenses
3] Collagen cross-linking
4] Intra corneal rings
5] Keratoplasty procedures
6] Phakic IOLs
7] Refractive lens exchange
8] Combinations - Intracorneal rings + collagen cross-linking
Intracorneal rings + Phakic IOLs
PTK + Intracorneal rings + Collagen cross-linking

Contact lenses – Rigid Gas Permeable Contact Lenses [RGP-CL] correct irregular astigmatism produced by the abnormal corneal shape and significantly improves the best corrected visual acuity.

Keratoconus is typically managed by a variety of rigid contact lens fitting techniques and lens designs. The two most fundamental fitting techniques are apical corneal touch (including divided or three-point touch) and apical clearance. The information provided by corneal topography can help in selecting appropriate initial trial contact lenses.

A standardized keratoconus fitting protocol which was developed by the CLEK study can simplify contact lens management in patients with mild to moderate keratoconus. All contact lens parameter options are uniform except for base curve and secondary curve radii, which are determined by interpretation of fluorescein patterns. The initial trial lens's base curve is the average keratometric reading; sequentially steeper lenses are applied until definite apical clearance is observed. Despite the potential risk for corneal scarring imposed by flat-fitting [apical touch] rigid contact lenses, most patients wear flat-fitting lenses as was demonstrated in the CLEK Study.

Piggy back lenses [RGP-CL over a soft CL] can be used in patients who are uncomfortable with RGP wear, more so in those who are prone for epithelial erosion at the apex of cone.

Rose-K design RGP lenses are specially designed for keratoconic eyes with a diagnostic set comprising of 26 lenses with base curves ranging from 5.1 to 7.6 mm in 0.1 mm increments, a standard lens diameter of 8.7 mm. It is among the most popular custom-made lenses for keratoconus and provides a better fit and visual performance. Jain AK and Sukhija J in a study of 38 eyes found that Rose-K design lenses are successful in visually rehabilitating 100% of moderate and 96% of severe keratoconus eyes. In their series on Indian eyes, most patients (90%) maintained contact lens wear comfort. Also, corneal curvature on axial maps of videokeratography is a better predictor of base curve of final fit contact lens.

Soper lens is another custom made lens which has two zones in the central posterior curvature. The central zone is designed to vault steep central area and is of varying steepness dependent on the patient's cornea. The peripheral zone is always manufactured with a 45 D curvature designed to vault slightly the relatively normal midperiphery and limbal cornea.

Boston Scleral Lens Prosthetic Device (BSLPD) provides clear vision and comfort to most patients who are intolerant to traditional lenses especially in advanced keratoconus. It is a fluid ventilated scleral lens designed to enclose a bubble free reservoir of fluid over the corneal surface. A series of breaches created between the haptic bearing surface of the lens and the underlying sclera facilitates the aspiration of surface tears into the reservoir so that intrusion of air bubbles during blink is prevented. The shape of haptic confirms exactly to that of underlying sclera to maintain functionality and prevents intrusion of air bubbles. It has the disadvantage that it is highly expensive [costs $5,000 for one and $7,600 for a pair] and requires a time-consuming care regimen. It is considered an option before surgery for those who can afford it.

Collagen cross-linking by Riboflavin and UV-A: Collagen cross-linking consists of photopolymerisation of collagen fibres by the combined action of a photosensitizing substance (riboflavin or vitamin B2) and ultraviolet type A rays from a solid state UV-A source. Photopolymerisation increases the rigidity of corneal collagen and its resistance to ectasia.

Under topical anaesthesia, a 7 mm circle is marked on the cornea using a Thornton marker and epithelium of the marked area scraped off using a blunt spatula. A few drops of a solution containing freshly prepared 0.1 % riboflavin and 20 % dextran is put on the cornea and left in place for 5 minutes. UV lamp is then turned on, after making sure that it is focused on the apex of cornea and left in place for 5 minutes. The lamp is then turned off, riboflavin-dextran solution again instilled, and 5 minute exposure repeated 5 times (total exposure 25 minutes, total treatment time 30 minutes). After treatment, eye is washed with Balanced Salt Solution, a drop of antibiotic and cycloplegic instilled and a Balanced Contact Lens applied.

After cross-linking, biomechanical studies have found an increase in corneal rigidity of 328.9% in human
corneas, mostly in the anterior stroma. There is an increase in collagen-fibre diameter and resistance to enzymatic digestion by collagenases. The UV-A light also produces apoptosis of ‘unhealthy’ activated keratocytes, in addition to being absorbed by riboflavin to strengthen the collagen. However, at 6 months repopulation of keratocytes occur in the anterior stroma. A mean reduction in Keratometry by 2.5D is noted after treatment. Though there are several studies which have found favourable outcome with this mode of treatment, Dresden Clinical Study has the maximum data base and longest follow-up. The 3 and 5-year results of the Dresden clinical study have shown that in all treated 60 eyes the progression of keratoconus was at least stopped (‘freezing’). In 31 eyes there also was a slight reversal and flattening of the keratoconus by up to 2.87 diopters. Best corrected visual acuity improved slightly by 1.4 lines. So far, over 150 keratoconus patients have received crosslinking treatment in Dresden. Laboratory studies have revealed that the maximum effect of the treatment is in the anterior 300 mm of the cornea. As for the corneal endothelium, a cytotoxic level for endothelium was found to be 0.36 mW/cm which would be reached in human corneas with a stromal thickness of less than 400 microns, which signifies the importance of preoperative pachymetry. Collagen crosslinking has the potential to become the standard therapy for progressive keratoconus in the future, diminishing significantly the need for corneal transplantation.

**Intracorneal rings**

Intracorneal rings act as passive spacing agents which flatten the central cornea. These crescentic inserts made of PMMA placed circumferentially in the cornea were used initially for the treatment of low myopia. The amount of correction achieved is dependent on ring thickness, thicker the ring more the correction. On insertion they shorten the arc length of the anterior corneal surface, iron out gross irregularities and in effect create a ‘second limbus’. They are placed within the cornea at 65–70 % depth to lift the superior or inferior ectasia. Patients who are contact lens intolerant with central clear cornea are ideal candidates. In stage 4 also rings can be employed if the apical scar is localized and is amenable to phototherapeutic keratectomy. Among the various intracorneal rings namely Kerarings, INTACS and Ferrara rings, INTACS [Addition technology] has been most extensively studied.

In the pre-operative assessment, in addition to routine work-up, ultrasonic pachymetry at multiple locations and corneal topography is done preferably using Pentacam or Orbscan. After preparation as in routine anterior segment surgery under topical anesthesia, a small radial corneal incision (~1.0 mm in length) is made at 70 % depth, the outermost part of it, 1 mm central to the temporal limbus after ensuring centration. Two intrastromal tunnels (clockwise and counterclockwise) are created using specialized instruments. For INTACS insertion, tunneling is done after ensuring that vacuum is built up. The segments are then inserted and a suture is put. The selection of segment is based on standard nomograms. In a global or central cone two rings of same thickness are inserted while in an asymmetrical cone, one thin segment in the flatter area which is usually superior and one thicker segment in the steeper area which is usually inferior is done. In peripherally located cones, inferior segment alone may be more beneficial than 2 segments.

In the largest series by Colin J et al, a prospective study of 100 eyes with clear central corneas which underwent INTACS insertion found that, at two years UCVA and BCVA improved in 80.5 % and 68.3 % of eyes respectively. Preoperatively 22 % had a BCVA of 20/40 or better while postoperatively 53.7 % had the same. The mean keratometry readings decreased from 50.1±5.6 D preoperatively to 46.8±4.9 D at two years follow-up. Contact lens tolerance was restored in over 80 % of cases. In 4 eyes INTACS were removed without complications due to dissatisfaction with visual symptoms related to ring edges.

**Complications**

Keratoplasty procedures: As recipient pathology, keratoconus has the distinction of enjoying excellent results following penetrating keratoplasty. Kirkness et al. reported 97% graft clarity at 4 years in 1990 and Beckingsale P et al reported 98% graft clarity at 5 years. Using same-sized trephine for both donor and recipient can reduce postoperative myopia in patients with highly myopic refraction.

Anterior deep lamellar keratoplasty (DALK) has the advantage that it is an extra ocular procedure. There is less endothelial damage and minimal chance of rejection and so lesser steroid requirement. The globe is tectonically stronger and earlier stable refraction can be expected. In their large series of 181 eyes, Anwar M et al found that 89% achieved 20/40 or better vision, while only 10% achieved 20/20 at 6 months follow-up after Anterior Deep Lamellar Keratoplasty. Watson SL et al in a retrospective case-control study of 47 eyes, of which 27 underwent DALK and 25 underwent PK for keratoconus, found that at 55 months follow-up, mean BCVA was 6/6 in PK group while it was 6/9 in DALK group. Funnell CL also found similar results though two eyes in the PK group experienced rejection. Thus, with visual outcome almost similar to full thickness procedure, DALK has probably become the procedure of choice in young keratoconus patients as the risk of immunological rejection is minimal. However, this cannot be performed when there is a dehiscence in Descemet’s membrane as in an eye which had hydrops.

Excimer laser assisted anterior lamellar keratoplasty uses excimer laser for ablating corneal stroma to the desired depth in both donor and recipient. Procedures like phakic IOL or refractive lens exchange could be considered for refractive correction once refractive stability is achieved. However ultrasound pachymetry can be inaccurate in up to one-third of cases. A variety of combination treatments are being tried, aimed at refractive correction, but with little long term follow-up. Combination of collagen cross linking and Intacs can give better results than Intacs insertion alone. The same may be combined with phototherapeutic keratectomy in cases with prominent apical scarring. Similarly, phakic IOL may be combined with Intacs to better deal with ametropia seen in keratoconus.

Conclusion

The last decade has witnessed revolutionary advances in the field of keratoconus. Intracorneal ring to a good extent is capable of dealing with gross corneal asymmetry, so that contact lens wear can be resumed, though not universally applicable. With the resurgence of Deep Anterior Lamellar Keratoplasty the risk of immunological rejection has become minimal, prompting surgeons to offer this option early so that patients with advanced disease have better long term visual outcome and better quality of life.

Years of painstaking basic research has found clinical application in the form of collagen cross linking using riboflavin and ultraviolet-A radiation, which is seen to arrest disease progression, at least for a few years and to some extent improve the mean keratometry values. If long term refractive stability is assured, the future is likely to see an explosive increase in refractive surgical procedures like phakic IOLs or refractive lens exchange.

References


